

Figure 1.—The photomicrograph of the splenectomy specimen shows a noncaseating granuloma (original magnification $\times 200$).

A course of prednisone, 80 mg per day, was started, and the platelet count increased to 152×10^9 per liter over the following week. Four weeks later, as the corticosteroid dosage was being reduced, thrombocytopenia recurred. The patient, therefore, underwent splenectomy. After the operation, the platelet count increased to normal, allowing discontinuation of the prednisone therapy.

The spleen weighed 264 grams and contained typical noncaseating granulomata with hyalinization, consistent with a diagnosis of sarcoidosis (Figure 1). The red pulp contained foamy macrophages indicating platelet destruction. Mycobacterial and fungal stains and cultures were negative.

Discussion

Dickerman and co-workers reported 35 cases of thrombocytopenia associated with sarcoidosis.¹ The cases were divided into three groups by the severity of thrombocytopenia and type of bleeding. Group I comprised ten patients with a high frequency of bleeding due to esophageal varices and pancytopenia including moderate thrombocytopenia. Their platelet counts returned to normal following splenectomy, suggesting that congestive hypersplenism was the responsible mechanism. Six patients had chronic thrombocytopenia with mild to moderate bleeding episodes involving skin, mucous membranes, gingiva and genitourinary tract, usually over a long period of time. All had moderate to severe thrombocytopenia. Splenectomy resulted in clinical improvement in four patients. The remaining 19 patients had severe thrombocytopenia with an acute episode of bleeding involving many sites. Five died of intracerebral bleeding. The eight patients who underwent a splenectomy recovered. Seven similar cases have been reported since 1972,^{2,3,5-9} one patient dying of intracerebral bleeding.⁶

Our patient best fits the second group. He had isolated thrombocytopenia for 6½ years with only infrequent minor bleeding episodes before the recent diagnosis of sarcoidosis. He required splenectomy to control his thrombocytopenia.

The results of platelet-associated IgG assays have been reported in four thrombocytopenic patients with sarcoidosis.^{2-4,9} It was reported to be weakly positive in one case, but the titer and the assay used were not reported.³ In another case,² the platelets were treated with paraformaldehyde, which may result in falsely elevated values.¹⁰ The assay was reported to be positive in one other case, but the details of that

case were not included in the report.⁴ The assay was negative in one other patient.⁹

The presence of increased platelet-associated IgG, megakaryocytic hyperplasia and a good response to corticosteroid therapy and splenectomy suggest that the thrombocytopenia was due to immune destruction in this patient.

Whether sarcoidosis and thrombocytopenia are causally related or coincidental events is unclear, in spite of the mentioned case reports. A systematic survey of the incidence of thrombocytopenia in sarcoidosis will be required to determine whether this association exists or not.

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Atypical Diffuse Angiosarcoma of the Liver

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ANGIOSARCOMA is the most common primary malignant mesenchymal tumor of the liver; yet, its incidence is exceptionally low, ranging from 0.002% to 0.013% in autopsy series.^{1,2} Only two prior cases in 96,000 autopsies have been encountered at Los Angeles County-University of Southern California (USC) Medical Center. Hepatocellular carcinoma is 30 to 81 times more frequent²; because angiosarcoma usually presents with signs and symptoms of chronic liver disease and initial workup often shows evidence of hepatic masses, hepatocellular carcinoma is commonly considered. Peritoneoscopy may confirm the presence of single or multiple hepatic lesions that are usually hemorrhagic, and open liver biopsy most often leads to a correct diagnosis.³

To our knowledge, this is the first report of a case of

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ABBREVIATIONS USED IN TEXT

CEA = carcinoembryonic antigen
 CT = computed tomography
 USC = University of Southern California

angiosarcoma of the liver uniformly and diffusely involving all aspects of all lobes. The tumor was not diagnosed antemortem despite extensive investigation, in large part because this type of hepatic lesion had not previously been described. The diagnosis was open to question even at autopsy, confirmed only after morphologic, immunohistochemical and electron-microscopic examination.

Report of a Case

The patient, a 37-year-old computer engineer, was referred to the USC Liver Unit at Rancho Los Amigos Medical Center with a history of jaundice and a 7-kg (15-lb) progressive weight loss for two months and peripheral edema for two weeks. He was well until one year previously, when he was noted to have gastroesophageal reflux and esophagitis at endoscopy, for which treatment with metoclopramide hydrochloride was prescribed. No varices were seen. There was no history of jaundice, alcohol excess, intravenous drug abuse, transfusions, homosexuality or long-term use of anabolic steroids or other medications. Family history was negative for liver disease. There was no exposure to toxins such as vinyl chloride, arsenicals or thorotrast (colloidal preparation of thorium dioxide); his occupation did not involve exposure to other chemicals.

On physical examination he had recent muscle wasting, multiple spider angiomas over the chest and arms, peripheral pitting edema, deep jaundice and a palpable, firm liver extending 5 cm below the costal margin at the epigastrium and 3 cm at the midclavicular line. Minimal ascites was present, and distended abdominal wall veins were noted; no bruits were heard over the liver. Abnormal laboratory test results included the following: serum albumin level 26 and globulin 29 grams per liter; alkaline phosphatase 320 (normal < 104), serum aspartate aminotransferase 52 (normal < 34) and alanine aminotransferase 24 units per liter (normal < 34), total serum bilirubin level 622.4 μmol per liter (normal < 20.5), with direct bilirubin 432.6 μmol per liter, and prothrombin activity 60%. Hepatitis B surface antigen and α -fetoprotein were undetectable. Carcinoembryonic antigen value (CEA) was 33 μg per liter (normal < 5.0). The complete blood and platelet counts were normal.

Investigations before referral showed a normal liver with a large caudate lobe on computed tomographic (CT) scan and a normal transhepatic cholangiogram. A needle biopsy specimen showed pronounced sinusoidal dilatation and congestion. Hepatic vein catheterization done to exclude a venous outflow obstruction (Budd-Chiari syndrome) showed patent hepatic veins with an abnormal sinusoidal opacification. After transfer to the Liver Unit, a technetium Tc 99m sulfur colloid liver-spleen scan showed diffuse hepatomegaly with substantial redistribution without focal defects. At peritoneoscopy, the liver appeared red-black with turgid, large, irregular nodularity and increased superficial vascularity; many collateral veins were present on the falciform ligament and peritoneum. A liver biopsy specimen showed pronounced sinusoidal dilatation and rare atypical cells within the sinusoidal regions. The biopsy was not accompanied by excessive

bleeding. His condition deteriorated subsequently, with the total bilirubin level rising to 778 μmol per liter and prothrombin activity falling to 38%. Progressive renal failure and encephalopathy developed, and he died of massive gastrointestinal bleeding four weeks after referral to the Liver Unit.

Autopsy Findings

A postmortem examination was done 2½ hours after death. The liver was hypertrophic (3,050 grams) and uniformly deep red-purple. Glisson's capsule contained multiple thin fibrous septa on the surface of both the right and left lobes, giving a slightly nodular appearance. On cut section the parenchyma was uniformly hemorrhagic and spongiform, with diffuse involvement of all aspects of all lobes (Figures 1 and 2). The poorly defined cystic spaces of the spongy parenchyma ranged from pinpoint to 3 mm in diameter and were filled with unclotted blood. Only an occasional cystic space was larger, these larger spaces predominantly subcapsular and never greater than 1 cm in diameter. No nodules were

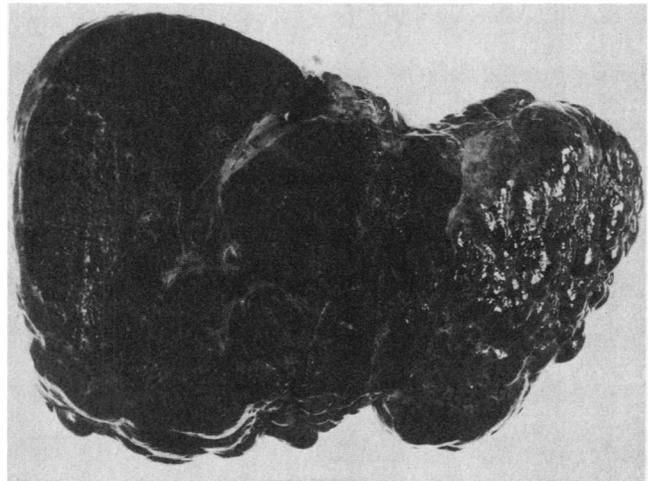


Figure 1.—The photograph of the gross liver specimen shows the external and cut surfaces of the hepatic angiosarcoma, with superficial nodularity but uniformity and absence of masses within the parenchyma.

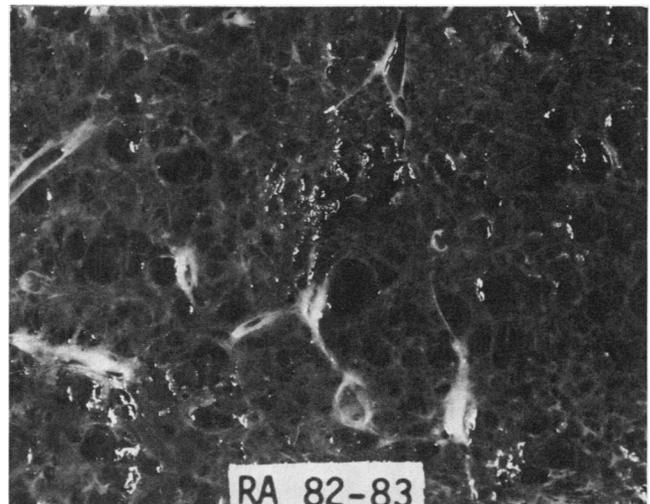


Figure 2.—Hepatic angiosarcoma is shown, with a hemorrhagic and spongiform pattern throughout all aspects of all lobes, the cysts pinpoint to 3mm in diameter.

present. Recognizable parenchyma was peripherally located around the cysts and was dark red-green. The subcapsular fibrous septa extended into the underlying parenchyma no deeper than 3 mm, with no subcapsular nodule formation.

Other pertinent findings included 2+ esophageal varices and 1,000 ml of bright red blood within the stomach, variceal bleeding being the immediate cause of death. The abdominal cavity contained 2.7 liters of clear yellow ascitic fluid, with no blood or blood clot formation. The spleen was slightly enlarged (260 grams). Lymphadenopathy was not present, and there was no evidence of a neoplasm in other organ systems.

The liver showed various patterns of morphologic change. Sinusoids were greatly dilated, often merging into cystic and cavernous regions. Hyperplasia and hypertrophy of the sinusoidal lining cells were prominent. Variable degrees of hepatocellular atrophy, with an increase in perisinusoidal reticulum and collagen, were present in these cords. This change often led to total disappearance of the liver cells, with their complete replacement by collagen.

Adjacent to the cystic regions, the sinusoids remained dilated, but showed a striking increase and atypicality of the lining cells, which often became multilayered (Figure 3). The cells were oval to fusiform, contained enlarged, hyperchromatic nuclei (Figure 4) and often formed solid regions containing abundant numbers of anaplastic cells. Mitotic figures and bizarre, multinucleated cells were present but infrequent. Small vascular channels composed of tumor cells were present in sinusoids and solid foci.

There was considerable cholestasis in the parenchyma least involved by tumor. The sinusoids contained varying numbers of inflammatory cells, predominantly macrophages and neutrophils. Rare foci of extramedullary hematopoiesis, a change sometimes seen in hepatic angiosarcomas, were present. There were also scattered, single, greatly hyperchromatic tumor cells within these regions. Tumor was not present in tissue sections of other organs.

A number of different antigens were stained by the immunoperoxidase technique. Factor VIII-related antigen showed focally but intensely positive intracytoplasmic granules in both the hyperplastic sinusoidal lining cells and the distinctly malignant tumor cells (Figure 5). There was strong CEA staining in bile canaliculi, but not in the cytoplasm of liver cells. There was no staining of tumor cells for CEA or α -fetoprotein. Fibrinogen was minimally present along the pericollagenous sinusoidal borders, but was not intracytoplasmic. Staining for albumin and prealbumin was negative.

Electron microscopy showed pertinent general features. There was an increase in considerably atypical sinusoidal lining cells exhibiting irregularity in nuclear size and shape, often containing prominent nucleoli. Chromatin tended to be condensed toward the nuclear border. Intracellular organelles were scanty. No Weibel-Palade bodies, distinctive for endothelial cells, or secretory material was present. Where tumor cells were particularly numerous within fibrous regions or dilated sinusoids, new small neoplastic vascular channels, sometimes containing erythrocytes (Figure 6), were present. There was no suggestion of an epithelial origin for these tumor cells.

Discussion

Although angiosarcoma is a very rare hepatic neoplasm, enough data have been accumulated over the years to show its

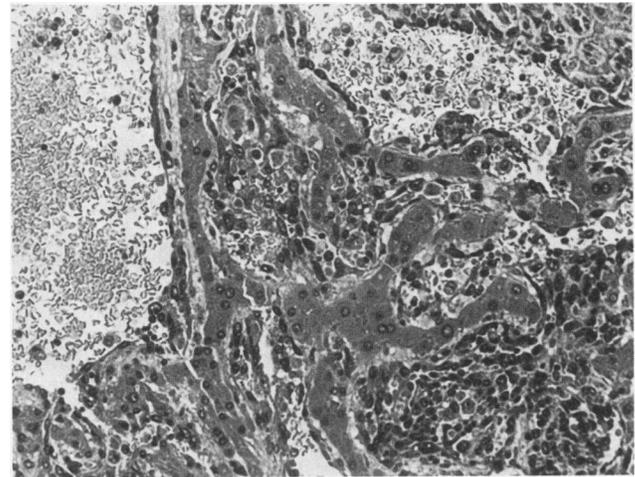


Figure 3.—The photomicrograph shows hepatic angiosarcoma, with pronounced dilatation of sinusoids, endothelial hyperplasia and proliferation of multilayered tumor cells. Moderate hepatocellular atrophy is present (hematoxylin and eosin stain $\times 255$).

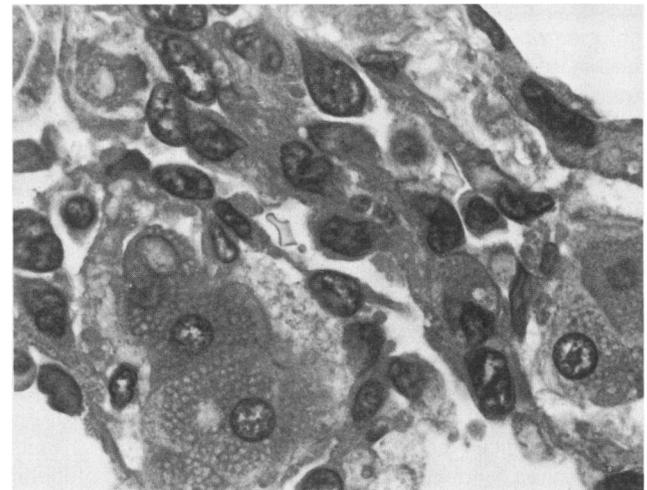


Figure 4.—The photomicrograph shows hepatic angiosarcoma, with enlarged, hyperchromatic tumor cells. The foamy cytoplasm in adjacent hepatocytes stained positively for fat (hematoxylin and eosin stain $\times 1,594$).

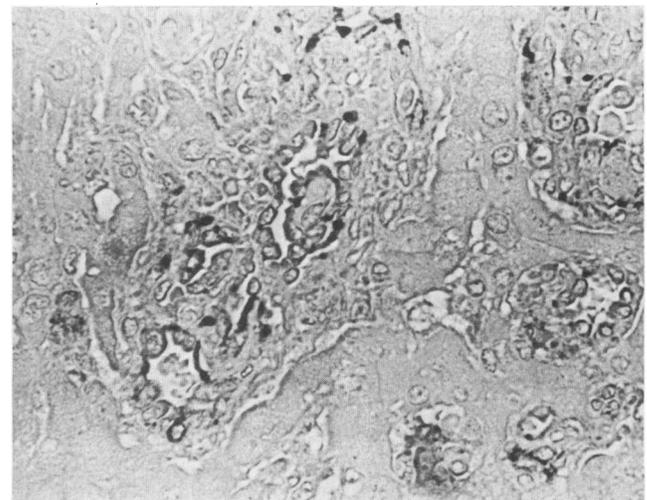


Figure 5.—Dark brown granular cytoplasmic staining is present in tumor cells, representing the presence of factor VIII-related antigen (immunoperoxidase stain $\times 680$).



Figure 6.—The electron micrograph shows a dilated sinusoid containing a small vascular channel formed by tumor cells, partially surrounded by collagen fibers ($\times 3,600$).

distinct association in humans with long-term exposure to numerous substances such as thorotrast, vinyl chloride and arsenicals.³ Reports of the tumor have also been documented with long-term usage of oral contraceptives,⁴ diethylstilbestrol,⁵ androgenic-anabolic steroids,⁶ exposure to radium⁷ and in patients with hemochromatosis.⁸ In most cases, as represented in this report, there have been no identifiable agents or toxins.³

Macroscopic examination of these tumors characteristically shows many hemorrhagic nodules that usually involve both lobes. The nodules may range from pinpoint to several centimeters in diameter. Large single masses are unusual. Cut sections show the nodules to be cavernous and cystic, filled with blood or gray-white with hemorrhagic borders. Larger hemorrhagic nodules may show spongiform changes.¹

Our patient presented with features of advanced liver disease, portal hypertension and hepatic failure. His platelets were normal and disseminated intravascular coagulation was not present. The absence of specific defects on liver-spleen and CT scans was misleading, suggesting only chronic liver disease. The bizarre gross appearance at peritoneoscopy did not suggest the diagnosis, except that a diffuse process was evident. Angiography would have been revealing but was not

done because of a rapid deterioration in the patient's condition. Two uncomplicated percutaneous liver biopsies did not disclose the tumor; the macroscopic appearance at autopsy, with the spongiform change uniformly and diffusely affecting all lobes, made the diagnosis difficult initially.

The liver did, however, show morphologic and electron-microscopic features of an angiosarcoma. The confirming piece of evidence indicating the vascular endothelial origin of the neoplasm was factor VIII-related antigen in the cytoplasm of the cells. This protein is normally present in endothelial cells, megakaryocytes and platelets, and is commonly used as a marker for tumors of vascular origin.⁹ Although the antigen has recently been described in squamous cell carcinoma, transitional cell carcinoma with squamous differentiation and renal cell carcinoma,¹⁰ there was no suggestion of any of these neoplasms in this patient.

In conclusion, although morphologic examination of the liver at autopsy showed changes typical for primary angiosarcoma, the clinical and pathologic diagnostic difficulties centered around the unusual macroscopic features of the tumor. This is the first report of a case of hepatic angiosarcoma with massive and uniform involvement of the entire liver.

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